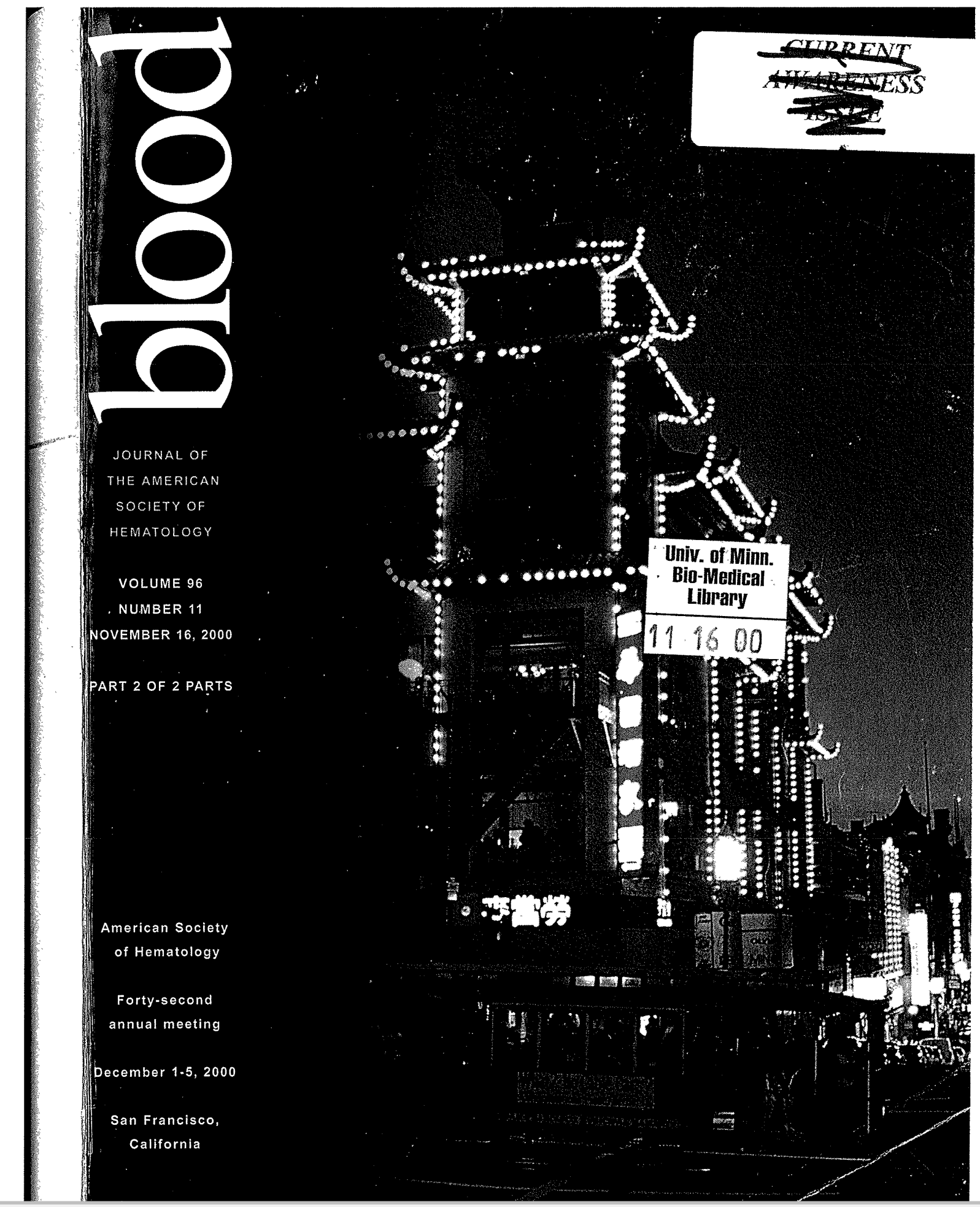
blood

JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

VOLUME 96
NUMBER 11
NOVEMBER 16, 2000

PART 2 OF 2 PARTS



American Society of Hematology

Forty-second annual meeting

December 1-5, 2000

San Francisco, California

Abstract# 4976

CLINICAL EFFICACY OF IRRADIATION IN CLL PATIENTS : PREDICTIVE VALUE OF *IN VITRO* RADIO-INDUCED APOPTOSIS. D Decaudin, J. Delic*, J. Dumont*, E. Blot*, G. Tertian*, B. Dubray*, C. Grandpeix*, J.M. Cosset*. *Department of Hematology, Laboratory of Radiopathology; Department of Radiotherapy, Institut Curie, Paris; Department of Hematology, Hôpital du Kremlin-Bicêtre, Le Kremlin-Bicêtre, France.*

Irradiation of CLL patients, formerly indicated as palliative treatment in case of bulky disease or hypersplenism, has been introduced since few years into myeloablative regimens. In order to discriminate patients for whom such treatment could be beneficial, we investigated the relationship between *in vitro* radio-induced apoptosis of leukemic cells and response to low-dose splenic or lymph node radiotherapy. Fourteen patients with CLL and receiving low-dose irradiation were included in the *in vitro* study The median time from diagnosis to radiotherapy was 60 months (range 5-156) Three patients were Binet Stage B and eleven patients were Binet stage C The median blood lymphocyte count prior to irradiation was 126 10^9/l (range 10-268). Irradiation was the first-line therapy in three cases, the second in seven cases, and the third in four cases Ten and five patients received splenic and tumor site irradiation, respectively, while one of them had received previous radiotherapy for a nasal site, followed by splenic irradiation 2 years later. Doses of radiotherapy ranged from 1 to 5 Gy Leukemic cells were analysed immediately after collection or 24 hours of culture following *in vitro* irradiation of 0 to 10 Gy. After Hoechst staining, the proportion of apoptotic cells was determined by fluorescence microscopy as the percent of cells presenting morphological characteristics of apoptosis, for a total number of 10^3. The tumor response rate was 47% with one complete remission and six partial remissions, three of which greater than 90% Excluding the patient receiving nasal irradiation without local recurrence, the mean duration of response was 3 months (range 1-4). For the ten patients receiving splenic irradiation, the tumor response rate was 40% with a mean percentage of decrease leukemic cells of 50%, 89 and 24% for responding and refractory patients, respectively ($p < 0.05$). The *in vitro* study showed a proportion of apoptotic leukemic cells ranged between 2 and 75%. We observed a high correlation between tumor response and *in vitro* tests ($p < 0.01$)(Mann-Whitney U test). After splenic irradiation, we also found a high correlation between the percentage decrease of leukemic cells and *in vitro* radio-induced apoptosis ($r = 0.87$, $p < 0.01$, Spearman correlation test). The positive predictive value (PPV) of the *in vitro* tests for tumor response was 100% at 2 Gy The PPV of the *in vitro* tests for hematological response was 75% at 2 Gy and 100% at 5 Gy. In this report, we observed a high correlation between *in vitro* radio-induced apoptosis of leukemic cells and clinical and hematological response to radiotherapy. These results suggest that the sensitivity of leukemic cells to irradiation should be first evaluated in an *in vitro* assay to spare refractory patients from the useless toxicity of TBI

Abstract# 4977

TREATMENT OF WALDENSTROM'S MACROGLOBULINEMIA WITH THALIDOMIDE. M.A. Dimopoulos, N. Viniou*, A. Zomas*, V. Grigoraki*, E. Galani*, C. Matsouka*, O. Economou*, N. Anagnostopoulos*, P. Panayiotides*. *School of Medicine, University of Athens, Athens , Greece.*

Thalidomide is an active agent in patients with refractory multiple myeloma. Based on these data we performed a phase II study in order to evaluate the activity of thalidomide in Waldenstrom's macroglobulinemia (WM) Thalidomide was administered on a dose-escalating schedule of 200 mg daily p o x 14 days with dose escalation by 200 mg every two weeks to a maximum dose of 600 mg. Twenty patients were treated with a median age of 74 years (range· 48 to 85 years) Hemoglobin was < 10.0 gr/dl in 5 patients, serum monoclonal IgM was >3.0 gr in 9 patients and lymphadenopathy and splenomegaly were present in 7 and 10 patients respectively. Ten patients were previously untreated, 1 was relapsing off treatment, 5 were primary refractory and 4 were treated during refractory relapse. Five patients (25%) achieved at least 50% reduction of serum monoclonal IgM and at least 50% reduction of tumor at all involved sites. At least 25% reduction of IgM was noted in all eventual responders within 4 weeks of thalidomide treatment. Responses occurred in 3 of 10 previoulsy untreated patients and in 2 of 10 pretreated patients. One responding patient with artial fibrillation died of an embolic cerebral accident 4 months after achieving a response and the other responding patients remain without progression for 2+ months to 12 + months Some degree of toxicity was observed in almost all patients. Grade 2 or 3 toxicities included constipation in 6 patients, somnolence in 3 patients, tremor in 2 patients and neuropathy in 2 patients This explained the inability to reach the targeted dose of thalidomide 600 mg p.o QD in all but 4 patients, the median daily dose of this agent was 200 mg We conclude that thalidomide has moderate activity in WM. A relatively low median daily dose could be administered to this elderly patient population.

Abstract# 4978

THALIDOMIDE AND DEXAMETHASONE COMBINATION FOR MULTIPLE MYLEOMA REFRACTORY TO DEXAMETHASONE-BASED REGIMENS. M.A. Dimopoulos, K. Zervas*, E. Galani*, V. Grigoraki*, E. Vervessou*, E. Samantas*, C. Kiamouris*, D. Gika*, C. Papadimitriou*, N. Anagnostopoulos*. *School of Medicine, University of Athens, Athens, Greece.*

Recent data suggest that thalidomide is active in approximately 30% of patients (pts) with refractory multiple myeloma. Between 7/99 and 7/00 we treated 38 pts with refractory myeloma with thalidomide 200 mg PO q h s, increased to 400 mg after two weeks (in absence of severe side effects), and intermittent dexamethasone 40 mg p.o. x 4 days on days 1-4, 9-12, 17-20 followed by monthly dexamethasone (days 1-4). Pts median age was 67 years (49 to 79 years) Immediately prior therapy has consisted of high-dose pulse dexamethasone (21 pts) or VAD (17pts). Twelve pts had previously received an autologous stem cell transplant Fourteen pts were considered as primary refractory and 24 pts were treated during refractory relapse. Serum b2-microglobulin > 3 0 mg/dl was present in 66% of pts and elevated serum LDH in 26% Among the 33 patients evaluable for response so far, 17 (52%) have achieved a partial response defined by reductions > 50% of serum monoclonal protein and/or by >75% of urine monoclonal protein The time to response was short (median: 1.5 months, range 0.5 to 3 months). Side effects included constipation (75%), morning somnolence (54%), tremor (25%), dry skin/rash (18%), headache (14%) and peripheral neuropathy (7%). Our results indicate activity of the combination of thalidomide with dexamethasone in pts with multiple myeloma refractory to dexamethasone-based regimens. Pts accrual and follow up is ongoing in order to define the activity of this combination in pts' subsets and to assess the duration of response

Abstract# 4979

THE ROLE OF BISPHOSPHONATES IN MULTIPLE MYELOMA: META-ANALYSIS OF PUBLISHED RANDOMIZED TRIALS. B. Djulbegovic,[1] K. Wheatley*,[2] M. Lacevic*,[1] G. Bos,[3] J Ross*,[4] H. Goldschmidt,[5] A. Glasmacher.[6] *[1]Blood and Bone Marrow Transplantation, H. Lee Moffitt Cancer Center, Univ. of South Florida, Tampa, FL, USA; [2]Clinical Trials Unit, Univ. of Birmingham, United Kingdom; [3]Dpt. of Internal Medicine, Univ. Hospital, Maastricht, The Netherlands; [4]Dpt. of Haematology, Northampton General Hospital, United Kingdom; [5]Dpt. of Internal Medicine V, Univ. of Heidelberg, Germany; [6]Dpt. of Internal Medicine I, Univ. of Bonn, Germany.*

Bisphosphonates (Bs) are increasingly used in the management of multiple myeloma (MM). **AIM:** To synthesize available knowledge about benefits and harms of Bs in MM, we performed meta-analysis (MA) of available published evidence **METHODS:** We identified 10 randomized, placebo controlled trials (RCTs), of which 9 trials served as a basis for this analysis (Bs. etidronate 2 trials, clodronate 4, pamidronate 2 , ibandronate 1). A small cross-over trial was excluded from the analysis. A total of 1058 patients treated with Bs and 1017 patients with placebo were included in analysis Heterogeneity among the trials was minimal for the major outcomes considered in analysis, thus allowing pooling of data in this MA. **RESULTS:** The published evidence demonstrated a beneficial effect of Bs on prevention of pathological vertebral fractures. On average for every 8 patients treated with Bs one patient will avoid a vertebral fracture during median follow-up of 22 5 months (range 4 to 24 months, OR=0.53, 95%CI 0.39-0.72, P=0.00005). There was no significant effect of Bs on non-vertebral fractures (OR=0.99, 95%CI 0.69-1.40, p=0.9). There was also a beneficial effect of Bs on bone pain with absolute risk reduction of 14% (95%CI ranges from 8%-19%), indicating that on average for every 7 patients treated with Bs one patient will not experience pain. We found no significant effect of Bs on hypercalcemia (OR=0.84, 95%CI: 0.6-1.16, P=0.3]. Administration of Bs was associated with non-significant increase of gastro-intestinal side (GI) effects (OR=1.28, 95%CI 0.95-1 74, P=0.11). We found no significant effect of Bs on overall mortality in MM (OR=0.97, 95%CI 0.86-1.09) Results did not change when subgroup analysis according to type of Bs was performed The major limitation of our study is that it has not included unpublished data or individual-patient data. **CONCLUSIONS:** Based on our review of available evidence, Bs reduce the probability of pathological vertebral fractures and bone pain associated with MM. Further evidence is needed to determine whether some Bs are more effective than others and whether Bs have an effect on mortality.

Abstract# 4980

A PHASE II STUDY OF FLUDARABINE (F) AND MITOXANTRONE (N) IN THE TREATMENT OF PREVIOUSLY UNTREATED B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA. Sari H. Enschede,[1] Parameswaran Venugopal,[1] Agnes L. Guevarra*,[1] Teresa M. O'Brien*,[1] Stephanie A. Gregory.[1] *[1]Section of Hematology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, USA.*

Fludarabine alone is an effective initial induction therapy for CLL patients, with progressive/advanced disease, resulting in an overall response of 78% (Keating, *Blood* 1998). Mitoxantrone has well documented activity in lymphoid malignancies and may even act synergistically with other chemotherapeutic agents such as F The regimen of F, N and dexamethasone is effective for indolent NHL but immunosuppressive to the point of requiring infectious prophylaxis (McLaughlin, *JCO* 1966). In this study, we assessed the efficacy and toxicity of FN as initial induction treatment for CLL patients with stage II (progressive), III or IV disease. The median age was 58 (range 47-80) and M·F ratio of 2·1 Three patients (33%) had stage II disease, 2 patients (22%) had stage III, and 4 patients (45%) had stage IV disease Patients were treated with the regimen of F 25 mg/m^2 IV on days 1-3 and N 12 mg/m^2 on day 1 The cycles were repeated every 28 days for a maximum of 6 cycles Staging with CT scans and bone marrow studies were performed before and after treatment CR was defined as disappearance of all disease and bone marrow lymphocytes <30% PR was achieved if patients had a >50% reduction in measurable disease. A total of 11 patients were studied. Of the 9 evaluable patients, 4 (44%) achieved CR and 5 (56%) PR with 100% OR A total of 4 patients (3 CRs and 1 PR) progressed at 7, 10, 20 and 36 months; a median of 15 months. One patient progressed at 5 months but had received only 2 cycles of treatment A total of 4 patients (1 CR and 3 PRs) remain without progression at 8, 9, 25 and 27 months. The patient at 25 months had stable disease and underwent peripheral stem cell transplant at 20 months. The regimen was well tolerated and the adverse events were comparable to those from F alone. There were 3 hospitalizations for neutropenic fevers and most patients had grade 3-4 neutropenia. No antibiotic prophylaxis was required Although this was a small phase II study, it shows that the combination of FN is more efficacious (100% OR) but not more toxic than F alone in the upfront treatment for CLL patients The median time